



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Gerald McMAHON et al.

Title: HETEROARYLCARBOXAMIDE COMPOUNDS ACTIVE AGAINST  
PROTEIN TYROSINE KINASE RELATED DISORDERS

Appl. No.: 10/713,201

Filing Date: 11/17/2003

Examiner: Unassigned

Art Unit: 1641

**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.56**

Commissioner for Patents  
PO Box 1450  
Alexandria, Virginia 22313-1450

Sir:

The USPTO has waived the requirement under 37 CFR 1.98(a)(2)(i) to submit copies of U.S. patents and U.S. patent application publications when citing and submitting an Information Disclosure Statements in a patent application filed after June 30, 2003 and in an international application that has entered the national stage under 37 USC §371 after June 30, 2003. Accordingly, copies of these types of documents are not being supplied in connection with this application. Reference is being made to Final OG Notice from Office of Patent Legal Administration dated August 5, 2003, *Information Disclosure Statements May Be Filed Without Copies of U.S. Patents and Published Applications in Patent Applications filed after June 30, 2003.*

Applicants submit herewith on Form PTO/SB/08 a listing of the documents cited by or submitted to the U.S. PTO in parent application Serial No. 09/948,090, filed 09/07/2001, now U.S. Patent No. 6,316,479. As provided in 37 CFR §1.98(d), copies of the documents are not being provided since they were previously submitted to the United States Patent & Trademark Office in the above-identified parent application.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the

present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

**TIMING OF THE DISCLOSURE**

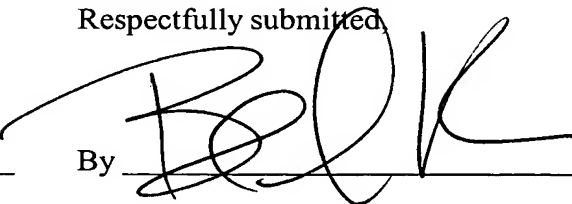
The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

Applicants respectfully request that the listed documents be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 CFR §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date April 19, 2004

By 

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 672-5475  
Facsimile: (202) 672-5399

Beth A. Burrous  
Attorney for Applicant  
Registration No. 35,087

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Substitute for form 1449B/PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

Use as many sheets as necessary)

Sheet 1 of 18

**Complete if Known**

Application Number	10/713,201
Filing Date	11/17/2003
First Named Inventor	Gerald McMAHON
Group Art Unit	1641
Examiner Name	Unassigned
Attorney Docket Number	034536-0684

**U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code <sup>2</sup> (if known)			
	A1	4,087,535		HEUBACH	05-02-1978	
	A2	4,284,786		KÄMMERER et al.	08-18-1981	
	A3	4,351,841		KÄMMERER et al.	09-28-1982	
	A4	4,965,276		BARTLETT et al.	10-23-1990	
	A5	4,992,271		FERNANDES et al.	02-12-1991	
	A6	5,217,999	A	LEVITZKI et al.	06-08-1993	
	A7	5,268,382	A	BARTLETT et al.	12-07-1993	
	A8	5,314,685	A	TYLE et al.	05-24-1994	
	A9	5,371,099	A	BARTLETT et al.	12-06-1994	
	A10	5,403,858	A	BASTARD et al.	04-04-1995	
	A11	5,476,866	A	KUO et al.	12-19-1995	
	A12	5,494,911	A	BARTLETT et al.	02-27-1996	
	A13	5,514,711	A	KITANO et al.	05-07-1996	
	A14	5,532,259	A	BARTLETT et al.	07-02-1996	
	A15	5,547,971	A	WEITHMANN et al.	08-20-1996	
	A16	5,573,775	A	ROBERTSON et al.	11-12-1996	
	A17	5,610,173	A	SCHWARTZ et al.	03-11-1997	
	A18	5,700,822	A	HIRTH et al.	12-23-1997	

**Examiner  
Signature**
**Date  
Considered**

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Sheet <span style="border: 1px solid black; padding: 0 10px;">2</span> of <span style="border: 1px solid black; padding: 0 10px;">18</span>				Attorney Docket Number		034536-0684

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	A19	5,700,823	A	HIRTH et al.	12-23-1997	
	A20	5,783,592	A	SCHWARTZ et al.	07-21-1998	
	A21	5,843,947	A	ROBERT et al.	12-01-1998	
	A22	Re. 36,256	E	SPADA et al.	07-20-1999	
	A23	5,932,602	A	HIRTH et al.	08-03-1999	
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	A27	6,022,884	A	MANTLO et al.	02-08-2000	
	A28	6,184,237	B1	MANTLO et al.	02-06-2001	
	A29	6,187,797	B1	PRUITT et al.	02-13-2001	
	A30	6,316,479	B1	McMAHON et al.	11-13-2001	
	A31	6,333,341	B1	MANTLO et al.	12-25-2001	

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		Office <sup>3</sup>	Number <sup>4</sup>	Kind Code <sup>5</sup> (if known)				
	A32	AU	31010/93	A	ZENECA LIMITED	07-22-1993		
	A33	DE	25 24 929	A1	HOECHST AG	12-16-1976		
	A34	EP	0 359 184	B1	BRISTOL-MYERS SQUIBB COMPANY	03-21-1990		

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Sheet	3	of	18	Attorney Docket Number	034536-0684

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	A35	EP	0 413 329	B1	ALCON LABORATORIES, INC.	02-05-1997		
	A36	EP	0 520 722	B1	ZENECA LIMITED	12-30-1992		
	A37	EP	0 522 937	A1	RHONE-POULENC RORER SA	01-13-1993		
	A38	EP	0 537 742	B1	MITSUBISHI CHEMICAL CORPORATION	08-21-1996		
	A39	EP	0 551 230	B1	ROUSSEL-UCLAF	07-19-1995		
	A40	EP	0 607 775	B1	HOECHST AKTIENGESELLSCHAFT	12-09-1998		
	A41	EP	0 607 776	B1	HOECHST AKTIENGESELLSCHAFT	12-09-1998		
	A42	EP	0 607 777	B1	HOECHST AKTIENGESELLSCHAFT	12-09-1998		
	A43	EP	0 645 145	B1	BRISTOL-MYERS SQUIBB COMPANY	03-12-1997		
	A44	EP	0 665 013	B1	AVENTIS PHARMA DEUTSCHLAND GmbH	10-24-2001		
	A45	EP	0 769 296	B1	AVENTIS PHARMA DEUTSCHLAND GmbH	07-04-2001		
	A46	EP	0 804 191	B1	SUGEN, INC. et al.	05-17-2000		
	A47	GB	2 240 104	A	FARMITALIA CARLO ERBA SRL	07-24-1991		
	A48	WO	87/04436	A1	LUNDBLAD	07-30-1987		
	A49	WO	91/17748	A1	HOECHST AKTIENGESELLSCHAFT	11-28-1991		

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	A50	WO	92/02444	A1	THE DOW CHEMICAL COMPANY	02-20-1992		
	A51	WO	92/18481	A1	RHONEPOULENC RORER INTERNATIONAL	10-29-1992		
	A52	WO	92/20642	A1	RHONEPOULENC RORER INTERNATIONAL	11-26-1992		
	A53	WO	92/21641	A1	PFIZER INC.	12-10-1992		
	A54	WO	94/26260	A1	YISSUM RESEARCH DEVELOPMENT COMPANY OF HEBREW UNIVERSITY OF JERUSALEM	11-24-1994		
	A55	WO	95/19169	A2	SUGEN, INC. et al.	07-20-1995		
	A56	WO	95/21613	A1	YISSUM RESEARCH DEVELOPMENT COMPANY OF HEBREW UNIVERSITY OF JERUSALEM	08-17-1995		
	A57	WO	96/33179	A1	SUGEN, INC.	10-24-1996		
	A58	WO	99/10325	A1	GLAXO GROUP LIMITED	03-04-1999		

NON PATENT LITERATURE DOCUMENTS			
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	A59	AAS et al., "Chloropromazine in combination with nitrosourea inhibits experimental glioma growth," <i>British Journal of Neurosurgery</i> 8(2):187-192 (1994).	
	A60	ANDREWS et al. (American Veterinary Medicine Association Panel on Euthana), "1993 Report of the AVMA Panel on Euthanasia," <i>J. American Veterinary Medicine Association</i> 202(2):229-249 (1993).	

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(use as many sheets as necessary)		<b>Attorney Docket Number</b>	034536-0684
Sheet	5	of	18

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	A61	BARTLETT et al., "Effects of leflunomide on immune responses and models of inflammation," <u>Springer Semin. Immunopathol.</u> 14:381-394 (1993).	
	A62	BARTLETT et al., "Leflunomide (HWA 486), a novel immunomodulating compound for the treatment of autoimmune disorders and reactions leading to transplantation rejection," <u>Agents and Actions</u> 32:10-21 (1991).	
	A63	BARTLETT et al., "Leflunomide: A novel immunomodulating drug in Nonsteroidal Anti-Inflammatory Drugs" 2nd ed. pp. 349-366, Lewis and Furstk eds., Dekker, NY, (1985).	
	A64	BARTLETT et al., <u>Chemical Abstracts</u> 116:128908, 1992	
	A65	BASERGA et al., "Antitumor Effects of Doxorubicin in Combination With Anti-epidermal Growth Factor Receptor Monoclonal Antibodies," <u>J. of Natl. Cancer Institute</u> 85(16):1327-1333 (1993).	
	A66	BAUDY et al., "Potent Quinoxaline-Spaced Phosphono alpha-Amino Acids of the AP-6 Type as Competitive NMDA Antagonists: Synthesis and Biological Evaluation," <u>J. Med. Chem.</u> 36:331-342 (1993).	
	A67	BILDER et al., "Tyrphostins inhibit PDGF-induced DNA synthesis and associated early events in smooth muscle cells," <u>Am. J. Physiol.</u> 260(Cell Physiol.29):C721-C730 (1991).	
	A68	BIRCHALL et al., "Compositions for killing internal parasites containing 3-teri-alkyl-4-hydroxy-5-halobenzylidene-malononitriles," <u>Chemical Abstracts</u> 88:535 (1978).	
	A69	BRYCKAERT et al., "Inhibition of Platelet-Derived Growth Factor-Induced Mitogenesis and Tyrosine Kinase Activity in Cultured Bone Marrow Fibroblasts by Tyrphostins," <u>Exp. Cell Research</u> 199:255-261 (1992).	
	A70	BUSTELO and BARBACID, "Tyrosine Phosphorylation of the vav Proto-Incogene Product in Activated B Cells," <u>Science</u> 256: 1196-1199 (1992).	
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	A72	CARBONI et al., "Cyanocarbon Chemistry. XI. Malononitrile Dimer," <u>J. Am. Chem. Soc.</u> 80:2838-2840 (1958).	
	A73	<u>Cecil Textbook of Medicine</u> , Eds: Wyngaarden, Smith, Bennett, W. B. Saunders p. 2220, (1992).	

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	A74	CHARETTE et al., "Contemporary approaches of chemotherapy," <u>Neuro-Oncology</u> , 7(1):135 (1995)		
	A75	CHEN and OKAYAMA, "Calcium Phosphate-Mediated Gene Transfer: A Highly Efficient Transfection System for Stably Transforming Cells with Plasmid DNA," <u>BioTech</u> . 6:632-638 (1988).		
	A76	CHERWINSKI et al., "The Immunosuppressant Leflunomide Inhibits Lymphocyte Progression Through Cell Cycle by a Novel Mechanism," <u>J. Pharmacology and Exp. Therap.</u> 227:460-468 (1995).		
	A77	CHONG et al., "Leflunomide, A Novel Immunomodulatory Agent: In Vitro Analyses of the Mechanism of Immunosuppression," <u>Transplant. Proc.</u> 25:747-749 (1993).		
	A78	CHONG et al., "Leflunomide, A Novel Immunosuppressive Agent," <u>Transplantation</u> 55:1361-1366 (1993).		
	A79	COGHLAN et al., <u>Chemical Abstracts</u> 123:285992, 1995		
	A80	CONN et al., "Purification of a glycoprotein vascular endothelial cell mitogen from a rat glioma-derived cell line," <u>Proc. Natl. Acad. Sci. USA</u> 87:1323-1327 (1990).		
	A81	DAINIPPON PHARM., <u>Chemical Abstracts</u> 72:12709, 1970		
	A82	DATI et al., "Inhibition of c-erbB-2 oncogene expression by estrogens in human breast cancer cells," <u>Oncogene</u> 5:1001-1006 (1990).		
	A83	DECKER and LOHMANN-MATTHES, "A quick and simple method for the quantitation of lactate dehydrogenase release in measurements of cellular cytotoxicity and tumor necrosis factor (TNF) activity," <u>J. Immunol. Methods</u> 115:61-69 (1988).		
	A84	EHRlich and BOGERT, "Experiments in the Veratrole and Quinoxaline Groups," <u>J. Org. Chem.</u> 12:522 (1947).		

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				Filing Date	11/17/2003
				First Named Inventor	Gerald McMAHON
				Group Art Unit	1641
				Examiner Name	Unassigned
Sheet	7	of	18	Attorney Docket Number	034536-0684

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	A85	FERRIS et al., "Synthesis of Zuinazoline Nucleosides from Ribose and Anthranilonitrile. Application of Phase-Transfer Catalysis in Nucleoside Synthesis," <u>J. Org. Chem.</u> 44(2):173-178 (1979).		
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	A89	FUMIHIRO "Injection Containing Etoposide," Application no. JP60239415 published Nov. 28 1995.		
	A90	GAZIT et al., "Tyrphostins. 1. Synthesis and Biological Activity of Protein Tyrosine Kinase Inhibitors," <u>J. Med. Chem.</u> 32:2344-2352 (1989).		
	A91	GAZIT et al., "Tyrphostins. 2. Heterocyclic and alpha-Substituted Benzylidenemalononitrile Tyrphostins as Potent Inhibitors of EGF Receptor and ErbB2/neu Tyrosine Kinases," <u>J. Med. Chem.</u> 34:1896-1907 (1991).		
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	A94	GOTTARDIS et al., "Estradiol-Stimulated Growth of MCF-7 Tumors Implanted in Athymic Mice: A Model to Study the Tumoristatic Action of Tamoxifen," <u>J. Steroid Biochem.</u> 30(1-6):331-314 (1988).	
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	A101	HOEKSTRA et al., "Differential effects of steurosporine and tyrphostins on receptor tyrosine kinase autophosphorylation and peptide substrate phosphorylation," <u>Experimental Therapeutics from 84th Annual Meeting of American Association for Cancer Research</u> , vol. 34, #2455 (1993).	
	A102	HONEGGER et al., "Point Mutation at the ATP Binding Site of EGF Receptor Abolishes Protein-Tyrosine Kinase Activity and Alters Cellular Routing," <u>Cell</u> 5:199-209 (1987).	

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	A103	HOUCK et al., "The Vascular Endothelial Growth Factor Family: Identification of a Fourth Molecular Species and Characterization of Alternative Splicing of RNA," <u>Molecular Endocrinology</u> 5:1806-1814 (1991).	
	A104	ISSIDORIDES and HADDADIN, "Benzofurazan Oxide. II. Reactions with Enolate Anions," <u>J. Org. Chem.</u> 31:4067-4068 (1966).	
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	A106	JU et al., "Leflunomide inhibits cytokine-induced DNA synthesis of rabbit synovial cells in culture," <u>Acta Pharmacological Sinica</u> 15:2232-26 (1994).	
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	A109	KARAMERIS et al., "Expression of Epidermal Growth Factor (EGF) and Epidermal Growth Factor Receptor (EGFR) in Gastric and Colorectal Carcinomas, An Immunohistological Study of 63 Cases," <u>Path. Res. Pract.</u> 189:133-137 (1993).	
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	A111	KIU et al., "Combination chemotherapy with carmustine and cisplatin before, during, and after radiotherapy for adult malignant gliomas," <u>Neuro-oncology</u> 25(3):215-220 (1995)	

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	A112	KOENDERS et al., "Epidermal growth factor receptor and prognosis in human breast cancer: a prospective study," <u>Breast Cancer Research and Treatment</u> 25:21-27 (1993).	
	A113	KORZENIEWSKI and CALLEWAERT, "An Enzyme-Release Assay for Natural Cytotoxicity," <u>J. Immunol. Methods</u> 64:313 (1983).	
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	A118	LEVITZKI, "Tyrphostins -- Potential Antiproliferative Agents and Novel Molecular Tools," <u>Biochem. Pharm.</u> 40(5):913-918 (1990).	
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	A121	LYALL et al., "Tyrophostins Inhibit Epidermal Growth Factor (EGF)-Receptor Tyrosine Kinase Activity in Living Cells and EGF-stimulated Cell Proliferation," <u>J. Bio. Chem.</u> , 264:14503-14509 (1989).		
	A122	MALKIN et al., "Phase I study of SU101, a novel signal transduction inhibitor, in recurrent malignant glioma," <u>Proc Annu. Meet Am. Soc. Clin. Oncol.</u> 16:A1371 (1997)		
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	A124	MANTLO et al., <u>Chemical Abstracts</u> 130:352186, 1999		
	A125	MARSHALL, E., "Search for a Killer: Focus Shifts from Fat to Hormones," <u>Science</u> 259:618-621 (1993).		
	A126	MATTAR et al., "Effect of leflunomide active metabolite, A771726, on signal transduction pathways necessary for proliferation," <u>Immunobiology</u> 186(1-2):43 (1992) (abstract).		
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	A128	MCCHESENEY et al., "An Evaluation of Leflunomide in the Canine Real Transplantation Model," <u>Transplantation</u> 57:1717-1722 (1994).		
	A129	MILLAUER et al., "High Affinity VEGF Binding and Developmental Expression Suggest Flk-1 as a Major Regulator of Vasculogenesis and Angiogenesis," <u>Cell</u> 72:835-846 (1993).		
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	A149	PLOWMAN et al., "Preclinical antitumor activity of temozolomide in mice: Efficacy against human brain tumor xenografts and synergism with 1,3-Bis(2-chloroethyl)-1-nitrosourea" <u>Cancer Research</u> 54(14):3793-3799 (1994)	
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	A157	ROSS, "The pathogenesis of atherosclerosis: a perspective for the 1990s," <u>Nature</u> 362:801-809 (1993).	

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	A158	RUSCH et al., "Differential Expression of the Epidermal Growth Factor Receptor and Its Ligands in Primary Non-Small Cell Lung Cancers and Adjacent Benign Lung," <u>Cancer Research</u> 53:2379-2385 (1993).	
	A159	RYGAARD and POVLSEN, "Heterotransplantation of a Human Malignant Tumour to Nude Mice," <u>Acta Path. Microbiol. Scand.</u> 77:758-760 (1969).	
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	A166	SHAFIE and GRANTHAM, "Role of Hormones in Growth and Regression of Human Breast Cancer Cells (MCF-7) Transplanted into Athymic Nude Mice," <u>J. Natl. Cancer Institute</u> 67(1):51-56 (1981).	

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	A174	Van UMMERSEN et al., "A phase I trial of SU101 in patients with solid tumors," <u>Proc. Annu. Meet. Am. Soc. Clin. Oncol.</u> 16:A740 (1997)	
	A175	WADA et al., "Anti-receptor antibodies reverse the phenotype of cells transformed by two interacting proto-oncogene encoded receptor proteins," <u>Oncogene</u> 5:489-495 (1990).	

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				Filing Date	11/17/2003
				First Named Inventor	Gerald McMAHON
				Group Art Unit	1641
				Examiner Name	Unassigned
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	A176	WALTENBERGER et al., "Different Signal Transduction Properties of KDR and Flt1, Two Receptors for Vascular Endothelial Growth Factor," <u>J. Biol. Chem.</u> 269:26988-26995 (1994).		
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